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(54) **2-Phenylpurinone derivatives, processes for their preparation, and their use as well as intermediates.**

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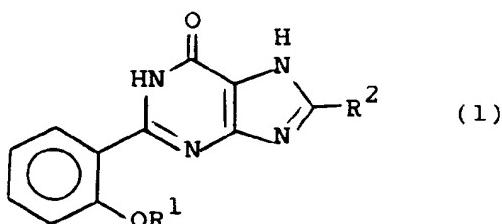
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**Description**

The present invention relates to purinone derivatives and in particular to such compounds having a substituted phenyl group at the 2-position of the purinone ring. This invention further relates to processes for their preparation, intermediates in their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combatting such conditions wherein such inhibition is thought to be beneficial. The compounds of this invention are bronchodilators and are therefore of use in combatting chronic reversible obstructive lung diseases such as asthma and bronchitis. In addition the compounds of the present invention exhibit anti-allergic activity and are therefore of use in combatting allergic diseases such as allergic asthma, allergic rhinitis, urticaria and irritable bowel syndrome. Furthermore the compounds of this invention are vasodilators and are therefore of value in combatting angina, hypertension and congestive heart failure.

Accordingly the present invention provides compounds of the formula (1) :

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and pharmaceutically acceptable salts thereof, wherein

25 R¹ is C<sub>1</sub>-<sub>6</sub>alkyl or C<sub>2</sub>-<sub>6</sub>alkenyl, and

R² is hydrogen or hydroxy.

Suitably R¹ is C<sub>2</sub>-<sub>5</sub>alkyl for example ethyl, n-propyl, isopropyl, butyl, isobutyl or pentyl.

Suitably R¹ is C<sub>3</sub>-<sub>5</sub>alkenyl for example allyl, butenyl or pentenyl.

Preferably R¹ is n-propyl.

30 Suitably R² is hydrogen. Suitably R² is hydroxy.

Particular compounds of this invention are :

2-(2-propoxyphenyl)-6-purinone,

2-(2-ethoxyphenyl)-6-purinone,

2-(2-butoxyphenyl)-6-purinone,

35 2-(2-isobutoxyphenyl)-6-purinone,

2-(2-propoxyphenyl)purine-6,8-dione,

2-(2-methoxyphenyl)purine-6,8-dione,

2-(2-ethoxyphenyl)purine-6,8-dione,

2-(2-butoxyphenyl)purine-6,8-dione,

40 2-(2-isobutoxyphenyl)purine-6,8-dione, and

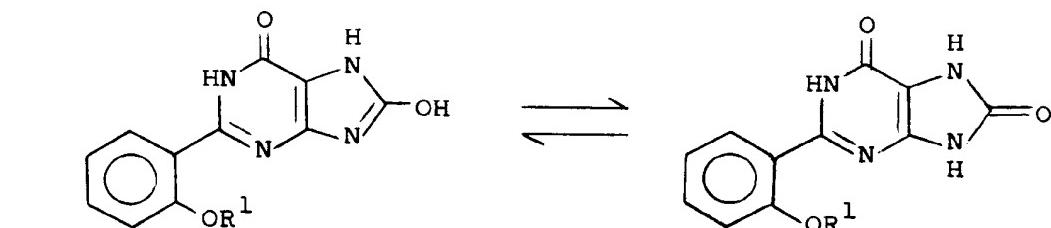
2-(2-allyloxyphenyl)purine-6,8-dione

and pharmaceutically acceptable salts thereof.

This invention covers all tautomeric forms of compounds of formula (1). For example the compound of the formula (1) wherein R² is hydroxy can exist in a tautomeric keto form :

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Compounds of the formula (1) wherein R² is hydrogen may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulphuric, phosphoric, acetic, citric, maleic, lactic, ascorbic, fumaric,

oxalic, methanesulphonic and ethanesulphonic acids.

Compounds of the formula (1) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, trans-dermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, starch, celluloses, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinyl-pyrrolidone, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycals, gelatins, cocoa-butter or other low melting vegetable waxes or fats.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 3 mg/Kg, and preferably from 0.005 mg/Kg to 1.5 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 1 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 12 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 4 mg/Kg, for example about 0.005 mg/Kg to 1 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered as required, for example from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. The compositions of the present invention have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, topically, rectally, parenterally or by inhalation. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium cromoglycate, histamine H<sub>1</sub>-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-arrhythmic agents for example quinidine, procainamide and lignocaine, calcium antagonists for example verapamil and nifedipine, diuretics such as thiazides and related compounds for example bendrofluazide, chlorothiazide, chlorothalidone, hydrochlorothiazide, and other diuretics

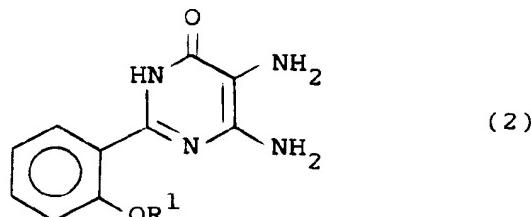
for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

In another aspect the present invention provides a process for the preparation of a compound of the formula (1) or a pharmaceutically acceptable salt thereof, which process comprises :

a) for compounds wherein R<sup>2</sup> is hydrogen, reacting a compound of the formula (2) :

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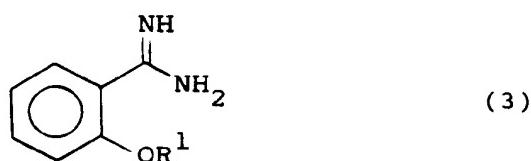
wherein R<sup>1</sup> is as hereinbefore defined, with a formylating agent;

b) for compounds wherein R<sup>2</sup> is hydroxy, reacting a compound of the formula (2) as hereinbefore defined with a carbonylating agent;

c) for compounds wherein R<sup>2</sup> is hydrogen, reacting a compound of the formula (3) :

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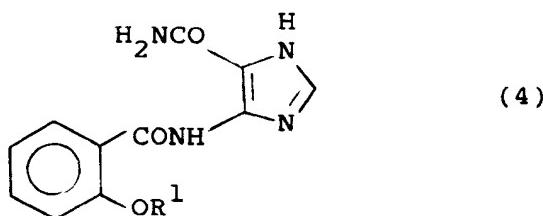


wherein R<sup>1</sup> is as hereinbefore defined with 4-amino-5-imidazolecarboxamide,

d) for compounds wherein R<sup>2</sup> is hydrogen, cyclising a compound of the formula (4) :

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wherein R<sup>1</sup> is as hereinbefore defined;

and thereafter optionally forming a pharmaceutically acceptable salt.

The reaction between a compound of the formula (2) and a formylating agent is conveniently performed in the absence of a solvent or in the presence of a suitable solvent such as a C<sub>1-4</sub>alcohol, pyridine or N-methylpyrrolidone, at ambient or elevated temperature, for example 50-250°C, preferably 100-200°C. Examples of formylating agents include formic acid, C<sub>1-4</sub>alkyl formate, formamide, C<sub>1-4</sub>alkyl formamide, formamidine, C<sub>1-4</sub>-alkyl formamidine or tri(C<sub>1-4</sub>)alkyl orthoformate. Suitably a compound of the formula (2) is reacted with formamidine acetate in the presence of sodium acetate. Preferably the compound of the formula (2) is used in the form of an acid addition salt, for example the sulphate, and is reacted with an excess of a formylating agent, for example formamide.

The reaction between a compound of the formula (2) and a carbonylating agent is conveniently performed in the absence of a solvent or in a suitable solvent such as a halohydrocarbon, pyridine or toluene, at ambient or elevated temperature, for example 50-250°C. Suitable carbonylating agents include urea, di(C<sub>1-4</sub>)alkylcarbonate, C<sub>1-4</sub>alkyl chloroformate, phosgene, trichloromethyl chloroformate or carbonyldiimidazole.

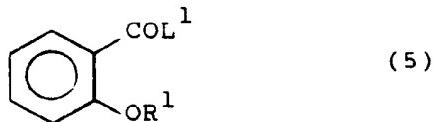
Suitably a compound of the formula (3) is reacted with an acid addition salt of 4-amino-5-imidazolecarboxamide, for example the hydrochloride, in the absence of a solvent or in a suitable solvent such as a C<sub>1-4</sub>-alcohol, pyridine or N-methylpyrrolidone at an elevated temperature, for example 50-250°C.

Suitably a compound of the formula (4) is cyclised by heating at an elevated temperature, for example 50-150°C, in the presence of an acid or a base in a suitable solvent such as aqueous C<sub>1-4</sub>alcohols, water, toluene,

a halohydrocarbon or acetonitrile.

A compound of the formula (4) can be prepared by reaction of 4-amino-5-imidazolecarboxamide with a compound of the formula (5) :

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wherein L¹ is halo and R¹ is as hereinbefore defined.

Suitably L¹ is chloro or bromo. Suitably a compound of the formula (5) is reacted with 4-amino-5-imidazolecarboxamide at ambient or elevated temperature e.g. 50-100°C in a suitable solvent such as toluene, acetonitrile or a halohydrocarbon e.g. chloroform or dichloromethane, optionally in the presence of a base such as pyridine or triethylamine, to form a compound of the formula (4) which may be cyclised *in situ* to form a compound of the formula (1) wherein R² is hydrogen or may be isolated and thereafter cyclised as hereinbefore described.

Compounds of the formulae (2) and (3) are known or preparable in conventional manner from GB Patent No 1338235.

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Pharmaceutically acceptable acid addition salts of the compounds of the formula (1) wherein R² is hydrogen may be prepared from the corresponding base of the compounds of the formula (1) in conventional manner. For example the base may be reacted with an acid in a C<sub>1-4</sub>alkanol, or an ion-exchange resin may be used. The salts of the compounds of the formula (1) may be interconverted using ion-exchange resins. Non-pharmaceutically acceptable salts are therefore of use as they can be converted to pharmaceutically acceptable salts.

Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

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### Bronchodilatation - In vivo

Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) were anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance was measured using a modification of the classical Konzett-Rossler technique (Versuchsanordnung zu Untersuchungen an der Bronchialmuskulatur. Naunyn-Schmiedebergs Arch. Exp. Path. Pharmak., vol 195: pp 71-74, (1940)). U46619 (9,11-methanoepoxy-PGH<sub>2</sub>) was infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test was administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction recorded.

The dose of compound required to reduce the U46619-induced bronchoconstriction by 50% is given as the BD<sub>50</sub>. These results demonstrate in vivo anti-bronchoconstrictor activity.

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COMPOUND OF EXAMPLE	BD <sub>50</sub> ( $\mu\text{mol/kg}$ )
1	3 . 6
2	6 . 5
3	3 . 8
4	5 . 3
5	1 . 0
7	3 . 6
8	1 . 5
9	4 . 5

20 **Vasodilatation - In vivo**

Male Wistar rats (300 g) were anaesthetised with a sodium 5-ethyl-5-(1-methylpropyl)-2-thiobarbiturate/sodium pentobarbitone mixture i.p. (62.5 and 22.5 mg/kg respectively). The trachea was cannulated and the rats breathed spontaneously air enriched with O<sub>2</sub> (5 ml/min). Blood pressure was recorded from a carotid artery and a jugular vein was cannulated for the administration of compounds. The temperature of the animal was maintained at 37°C by the use of an electric blanket. The abdominal aorta was separated from the inferior vena cava, distal to the renal arteries and was cannulated centrally to supply the perfusion pump with blood and distally for the perfusion of the hind quarters at constant pressure. The perfusion circuit was primed with 5% bovine serum albumin dissolved in 0.9% sodium chloride solution, pH adjusted to 7.4. Initially the pump rate was set between 10 and 15 ml/min to match the hind quarter perfusion pressure to that of the systemic circulation. Once set the pressure remained unaltered for the rest of the experiment. A change in the speed of the pump (equivalent to hindquarter blood flow) was used to assess the changes in hindquarter vascular resistance.

All compounds were administered as a bolus i.v. and from the dose response curves the dose required to produce a 50% increase in hindquarter blood flow (EDH<sub>50</sub>) was determined in  $\mu\text{moles/kg}$ . The following results were obtained :

COMPOUND OF EXAMPLE	EDH <sub>50</sub> ( $\mu\text{mol/kg}$ )
1	10 . 8
5	3 . 7

50 **Anti-allergic activity - in vitro**

Male Hartley strain guinea pigs (weighing 250-300 g) were actively sensitized to ovalbumin (OA) by a modified Herxheimer method (J. Physiol. 117:251-258, 1952). The animals were injected intramuscularly with 0.7 ml of a 5.0% OA solution prepared in isotonic saline. Four weeks after sensitization tracheas were removed and cut into spiral strips. Each trachea was cut in half, placed in 10-ml water-jacketed tissue baths and attached with biological tissue clips via silk suture to force displacement transducers for recording isometric tension. One half of each trachea served as a control for the corresponding drug-treated tissue. The tracheas were bathed in modified Krebs-Henseleit solution of the following composition (mM): NaCl, 118; KCl, 4.7; MgSO<sub>4</sub>, 1.2; CaCl<sub>2</sub>, 2.5; NaHCO<sub>3</sub>, 25; KH<sub>2</sub>PO<sub>4</sub>, 1.2; and glucose, 10. The physiologic buffer was maintained at 37°C and continually aerated with 95% O<sub>2</sub>/5% CO<sub>2</sub>. The tissue preparations were placed under 2 g passive tension and equilibrated

for 60 minutes, during which time they were washed every 15 minutes with fresh buffer. Each tissue was pre-treated for 45 minutes with meclofenamic acid (1  $\mu$ M).

Tissues were pretreated with the compound under test (100  $\mu$ M), or vehicle (0.4 mM NaOH) for 30 minutes prior to the addition of OA. OA (0.1  $\mu$ g/ml) was added to all tissues and the contraction was monitored for 15 minutes. Previous experiments indicated that this concentration of OA produced the maximum antigen-induced contraction. At the conclusion of the experiment, a maximally-effective concentration of carbachol (10  $\mu$ M) was added to each tissue and OA-induced responses were expressed as a percentage of this reference contraction. Since the compounds under test reduced basal tone, the absolute response (i.e., g tension) to carbachol was calculated as the difference between the tension after the addition of the test compounds and the maximum tension developed in the presence of carbachol. To evaluate effects of the test compounds, the degree of contraction was calculated 2 and 12 minutes after the addition of OA. OA-induced contraction of drug-treated tissues was expressed as a percentage of the response of vehicle-treated, paired controls.

When administered prior to OA challenge, both the compound of Example 1 (100  $\mu$ M) and the compound of Example 5 (100  $\mu$ M) significantly reduced basal tone. As a percentage of the maximum response to carbachol, the compound of Example 1 reduced basal tone by 17  $\pm$  3% and the compound of Example 5 by 24  $\pm$  7%. Administration of OA to vehicle-treated control tissues produced contractions which reached a maximum (67  $\pm$  2% of the maximum response to carbachol; N=4) within 3 minutes and were sustained over the 15-minute observation period. Two minutes after the addition of OA, the response of tissues treated for 30 minutes with the compound of Example 1 (100  $\mu$ M) was 78  $\pm$  12% (N.S., P > 0.05; N=4) of the control and the contractile response of those treated with the compound of Example 5 (100  $\mu$ M) was 79  $\pm$  3% (P < 0.05; N=4) of the control. Twelve minutes after OA challenge, contractile force had declined (P < 0.05) in tissues treated with either the compound of Example 1 or the compound of Example 5 to 46  $\pm$  9% or 60  $\pm$  4%, respectively, of the control values.

Results are expressed as a mean  $\pm$  S.E. of 4 experiments. Statistical significance of differences between the means of control and drug-treated groups was determined using a paired Student's t test.

These results indicate that compounds of Examples 1 and 5 inhibit antigen-induced contraction of the guinea-pig isolated trachea.

#### Anti-allergic activity - in vivo

Adult male albino Hartley strain guinea pigs weighing 400-600 g were actively sensitized to OA according to the procedure hereinbefore described. To measure pulmonary mechanics, a polyethylene catheter was inserted into the trachea of anesthetized (sodium pentobarbital, 35 mg/kg, i.p.) animals and airflow was measured via a heated pneumotachograph in combination with a differential pressure transducer connected to the pneumotachograph. Airflow and transpulmonary pressure signals were fed into an on-line pulmonary mechanics computer which integrated the flow signal to obtain tidal volume. Total pulmonary resistance ( $R_L$ ) and dynamic lung compliance ( $C_{DYN}$ ) were calculated at isovolumetric points according to the method of Amdur and Mead (Am. J. Physiol. 192:364-368, 1958).

A compound under test was dissolved in 25 mM NaHCO<sub>3</sub> plus one drop of polyethylene glycol 400 to a concentration of 100 mM. Based on the weight of the animal, the appropriate amount of solution was removed and the volume brought up to 1 ml with 25 mM NaHCO<sub>3</sub>. For the intraduodenal administration of test compounds, a small midline incision was made in the abdomen, the duodenum was exposed, and a butterfly needle attached to plastic tubing was inserted. All solutions were adjusted to the same volume (1 ml) and administered through the butterfly needle and followed with 0.5 ml of distilled water. The needle was then removed and the abdominal incision was stapled to prevent heat loss.

Aerosols of OA were generated to deliver approximately 0.375  $\mu$ l/breath. Pressure, flow rate and sensitivity were set such that a maximum pleural pressure of 20 cm water was attained during inhalation. One hour after the administration of the test compounds, guinea pigs were challenged with 5 inhalations of OA (0.5 mg/ml) via the tracheal cannula and changes in  $C_{DYN}$  and  $R_L$  were monitored for 10 minutes. Baseline values for  $C_{DYN}$  and  $R_L$  were 0.4-0.6 ml/cm water and 0.1-0.2 cm water/ml/sec, respectively.

Administration of OA to vehicle-treated, anesthetized guinea pigs produced bronchoconstriction which developed slowly over a 5-minutes period. Five minutes after OA challenge,  $R_L$  had increased 162  $\pm$  40% and  $C_{DYN}$  had decreased 51  $\pm$  26% (N=5). These changes in pulmonary function were stable over the remaining 5 minutes of the observation period. Intraduodenal administration of 100  $\mu$ mol/kg of the compound of Example 1 (N=4) 60 minutes before OA challenge significantly reduced antigen-induced bronchoconstriction: 5 minutes after challenge,  $C_{DYN}$  was unchanged from baseline (P < 0.01 vs. vehicle-treated controls) and the increase in  $R_L$  was limited to 51  $\pm$  26% (P < 0.05 vs. vehicle-treated controls).

Results are expressed as a mean  $\pm$  S.E. of 4 experiments. Statistical significance of differences between

the means of control and drug-treated groups was determined using a unpaired Student's t test.

#### Inhibition of Phosphodiesterase (PDE)

5 Eight pig hearts/lungs were collected from the abattoir and kept on ice until the pulmonary arteries or aortas could be dissected and excess fat removed. 120 g of tissue was dissected. Unless otherwise stated all procedures were done at 4° C. Following dissection arteries were flash frozen in liquid nitrogen and stored at -70° C until required. On the day of homogenisation, tissue was cooled with liquid nitrogen and broken into small pieces by striking with a hammer. The tissue was then homogenised in 15 mM BIS-TRIS, 1 µg/ml leupeptin and antipain, 2 µg/ml pepstatin A, 5 µM benzamidine, 2 mM EDTA (ethylenediaminetetraacetic acid) and 2 mM dithiothreitol, pH 6.5. Phenylmethanesulphonylfluoride (PMSF) was added to a final concentration of 50 µM just prior to homogenisation. The homogenate was then centrifuged for 20 minutes at 30,000 g. Supernatant was filtered firstly through glass wool and then a 0.45 µm filter. The resultant filtrate was then applied to a 60 ml DEAE-Sepharose<sup>R</sup> CL-6B (Diethylaminoethyl Cellulose with a bead size of 45-165 microns) (Pharmacia) column pre-equilibrated in homogenisation buffer. The column was washed with 150 mls of homogenisation buffer and PDE activities eluted with 150 ml of homogenisation buffer containing 100 mM sodium acetate. Six 25 ml fractions were collected, the flow rate throughout was 80 ml/hr.

10 20 Fractions 2 and 3 were pooled and BIS-TRIS, MgCl<sub>2</sub>, CaCl<sub>2</sub> added to final concentrations of 50 mM, 7 mM and 5 mM respectively. PMSF, leupeptin, antipain and pepstatin A were also added at the concentrations described above for these components. The pH of this pooled sample was corrected to 6.9.

15 25 The sample was applied, at a flow rate of 3 ml/hr, to a tandem column set up. The first column in the tandem was a 5 ml calmodulin-agarose column (Sigma) and the second a 1.5 ml cibacron blue 3GA-agarose column (Sigma). Both columns were pre-equilibrated with 50 mM BIS-TRIS, 5 mM MgCl<sub>2</sub>, 5 mM CaCl<sub>2</sub>, 5 mM benzamidine, 2 mM dithiothreitol pH 6.9. Following application of the sample the columns were washed with 20 ml of equilibration buffer.

20 The cibacron blue-agarose column was then disconnected and washed with a variety of buffers as indicated below (Buffer A = 50 mM BIS-TRIS, 5 mM benzamidine, 2 mM dithiothreitol pH 7.0).

25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 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4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585 4590 4595 4600 4605 4610 4615 4620 4625 4630 4635 4640 4645 4650 4655 4660 4665 4670 4675 4680 4685 4690 4695 4700 4705 4710 4715 4720 4725 4730 4735 4740 4745 4750 4755 4760 4765 4770 4775 4780 4785 4790 4795 4800 4805 4810 4815 4820 4825 4830 4835 4840 4845 4850 4855 4860 4865 4870 4875 4880 4885 4890 4895 4900 4905 4910 4915 4920 4925 4930 4935 4940 4945 4950 4955 4960 4965 4970 4975 4980 4985 4990 4995 5000 5005 5010 5015 5020 5025 5030 5035 5040 5045 5050 5055 5060 5065 5070 5075 5080 5085 5090 5095 5100 5105 5110 5115 5120 5125 5130 5135 5140 5145 5150 5155 5160 5165 5170 5175 5180 5185 5190 5195 5200 5205 5210 5215 5220 5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 6225 6230 6235 6240 6245 6250 6255 6260 6265 6270 6275 6280 6285 6290 6295 6300 6305 6310 6315 6320 6325 6330 6335 6340 6345 6350 6355 6360 6365 6370 6375 6380 6385 6390 6395 6400 6405 6410 6415 6420 6425 6430 6435 6440 6445 6450 6455 6460 6465 6470 6475 6480 6485 6490 6495 6500 6505 6510 6515 6520 6525 6530 6535 6540 6545 6550 6555 6560 6565 6570 6575 6580 6585 6590 6595 6600 6605 6610 6615 6620 6625 6630 6635 6640 6645 6650 6655 6660 6665 6670 6675 6680 6685 6690 6695 6700 6705 6710 6715 6720 6725 6730 6735 6740 6745 6750 6755 6760 6765 6770 6775 6780 6785 6790 6795 6800 6805 6810 6815 6820 6825 6830 6835 6840 6845 6850 6855 6860 6865 6870 6875 6880 6885 6890 6895 6900 6905 6910 6915 6920 6925 6930 6935 6940 6945 6950 6955 6960 6965 6970 6975 6980 6985 6990 6995 7000 7005 7010 7015 7020 7025 7030 7035 7040 7045 7050 7055 7060 7065 7070 7075 7080 7085 7090 7095 7100 7105 7110 7115 7120 7125 7130 7135 7140 7145 7150 7155 7160 7165 7170 7175 7180 7185 7190 7195 7200 7205 7210 7215 7220 7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 8225 8230 8235 8240 8245 8250 8255 8260 8265 8270 8275 8280 8285 8290 8295 8300 8305 8310 8315 8320 8325 8330 8335 8340 8345 8350 8355 8360 8365 8370 8375 8380 8385 8390 8395 8400 8405 8410 8415 8420 8425 8430 8435 8440 8445 8450 8455 8460 8465 8470 8475 8480 8485 8490 8495 8500 8505 8510 8515 8520 8525 8530 8535 8540 8545 8550 8555 8560 8565 8570 8575 8580 8585 8590 8595 8600 8605 8610 8615 8620 8625 8630 8635 8640 8645 8650 8655 8660 8665 8670 8675 8680 8685 8690 8695 8700 8705 8710 8715 8720 8725 8730 8735 8740 8745 8750 8755 8760 8765 8770 8775 8780 8785 8790 8795 8800 8805 8810 8815 8820 8825 8830 8835 8840 8845 8850 8855 8860 8865 8870 8875 8880 8885 8890 8895 8900 8905 8910 8915 8920 8925 8930 8935 8940 8945 8950 8955 8960 8965 8970 8975 8980 8985 8990 8995 9000 9005 9010 9015 9020 9025 9030 9035 9040 9045 9050 9055 9060 9065 9070 9075 9080 9085 9090 9095 9100 9105 9110 9115 9120 9125 9130 9135 9140 9145 9150 9155 9160 9165 9170 9175 9180 9185 9190 9195 9200 9205 9210 9215 9220 9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775 9780 9785 9790 9795 9800 9805 9810 9815 9820 9825 9830 9835 9840 9845 9850 9855 9860 9865 9870 9875 9880 9885 9890 9895 9900 9905 9910 9915 9920 9925 9930 9935 9940 9945 9950 9955 9960 9965 9970 9975 9980 9985 9990 9995 9999

50 **Phosphodiesterase Assay**

The assay was as described by Davis & Daly (1979) J. Cyclic Nucleotide Res., 5, 65-74, but with some modifications. The standard reaction mixture contained, in a final volume of 100 µl,

55 10 µM 5'-GMP (including 4000 dpm <sup>14</sup>C-GMP)  
 1 µM 3', 5'-cGMP (including 0.1 µCi <sup>3</sup>H-cGMP)  
 10 µM enzyme preparation  
 10 µM inhibitor dilution  
 and buffered with 50 mM TRIS/5 mM MgCl<sub>2</sub> pH 7.5. The reaction was initiated with enzyme, and was carried

out at 37°C for 5-10 minutes. The reaction was terminated by placing tubes in a boiling water bath for 2 minutes. 500 µM of 0.1 M HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) buffer pH 8.5 containing 0.1 M NaCl was then added to each assay tube and the contents applied to Affigel 601 (Bio-Rad) boronate affinity chromatography media (1.2 ml bed volume) which had previously been equilibrated with 10 ml of HEPES/NaCl buffer. Unreacted <sup>3</sup>H-cGMP was washed from the column with 10 × 1 ml HEPES/NaCl buffer. Labelled 5'-AMP was eluted into a scintillation vial with 6 ml 0.25 M acetic acid and counted in a scintillation counter using 10 ml Instagel (Packard). Recoveries were between 50%-75% as measured by recovery of <sup>14</sup>C-GMP. Assays were performed in duplicate and values corrected for blanks of <2%.

10 **Calculation of IC<sub>50</sub> values**

IC<sub>50</sub> values (the concentration of inhibitor required for 50% inhibition of activity) were obtained by incubation of the enzymes at 1 µM cyclic GMP and a range of inhibitor concentrations.

15	COMPOUND OF EXAMPLE	IC <sub>50</sub> (µM)
20	1	0.96
	2	4.49
	3	5.04
25	4	1.74
	5	1.25
	7	5.26
	8	6.79
30	9	3.64

35 **Example 1**

**2-(2-Propoxyphenyl)-6-purinone**

A stirred mixture of 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one sulphate (1.5 g) (prepared by the addition of concentrated sulphuric acid to an ethanolic solution of the free base) and formamide (15 ml) was heated in an oil bath (temp. 190°-200°C) for 70 minutes. When cool the mixture was filtered and the collected solid was washed with ethanol to give a crude product (1.1 g), m.p. 254-259°C, which was recrystallised from ethanol to give the title compound, 0.72 g, m.p. 263-265°C.

45 **Example 2**

**2-(2-Ethoxyphenyl)-6-purinone**

In a similar manner to Example 1 reaction of 4,5-diamino-2-(2-ethoxyphenyl)pyrimidin-6-one sulphate (1.5 g) with formamide (15 ml) afforded the title compound, 0.36 g, m.p. 276-277°C, (recrystallised from ethanol).

50 **Example 3**

**2-(2-Butoxyphenyl)-6-purinone**

55 In a similar manner to Example 1 reaction of 4,5-diamino-2-(2-butoxyphenyl)pyrimidin-6-one sulphate (1.5 g) with formamide (5 ml) afforded the title compound, 0.65 g, m.p. 247-248°C, (recrystallised from ethanol).

**Example 4****2-(2-Isobutoxyphenyl)-6-purinone**

5 In a similar manner to Example 1 reaction of 4,5-diamino-2-(2-isobutoxyphenyl)pyrimidin-6-one sulphate (1.4 g) with formamide (5 ml) afforded the title compound, 0.24 g, m.p. 272-273°C, (recrystallised from ethanol).

**Example 5****2-(2-Propoxyphenyl)purine-6,8-dione**

10 A mixture of 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one (1.3 g), and urea (1.5 g) was heated in an oil bath (temp. 190°C) for 45 minutes. The resultant solid was digested with hot water, the mixture filtered and the solid washed with water to give a crude product, 1.36 g. Recrystallisation from dimethylformamide gave 15 the title compound (1.01 g), m.p. >350°C, δ(DMSO-d<sub>6</sub>), 1.01 (t, 3H); 1.88 (m, 2H); 4.09 (t, 2H); 7.10, 7.21, 7.52 and 7.76 (multiplets, 4H); ca 11.07, 11.55 and 11.95 (very broad singlets, 3H).

**Example 6****2-(2-Methoxyphenyl)purine-6,8-dione**

20 In a similar manner to Example 5 reaction of 4,5-diamino-2-(2-methoxyphenyl)pyrimidin-6-one (0.93 g) with urea (1.20 g) afforded the title compound, 0.28 g, m.p. 329-330°C, (recrystallised twice from dimethylformamide).

25

**Example 7****2-(2-Ethoxyphenyl)purine-6,8-dione**

30 A solution of 4,5-diamino-2-(2-ethoxyphenyl)pyrimidin-6-one sulphate (2.0 g) in water (50 ml) was neutralized with ammonium hydroxide and extracted with chloroform. The organic extract was evaporated under reduced pressure to dryness and the residual free base was treated in a similar manner to Example 5 with urea (1.74 g) to afford after recrystallisation from dimethylformamide the title compound, 0.66 g, m.p. 349-351°C.

35

**Example 8****2-(2-Butoxyphenyl)purine-6,8-dione**

40 In a similar manner to Example 5 reaction of 4,5-diamino-2-(2-butoxyphenyl)pyrimidin-6-one (0.96 g) with urea (1.05 g) afforded the title compound, 0.26 g, m.p. 324-326°C, (recrystallised from dimethylformamide).

**Example 9****2-(2-Isobutoxyphenyl)purine-6,8-dione**

45

Carbonyldiimidazole (1.01 g) was added to 4,5-diamino-2-(2-isobutoxyphenyl)pyrimidin-6-one (1.50 g) in toluene (100 ml) and the resulting mixture was heated under reflux for one hour yielding a brown solid which was collected. This solid was washed with water and recrystallised from dimethylformamide to yield the title compound, 0.22 g, m.p. >360°C.

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**Example 10****2-(2-Allyloxyphenyl)purine-6,8-dione**

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4,5-Diamino-2-(2-allyloxyphenyl)pyrimidin-6-one sulphate (0.8 g) was added to a stirred solution of carbonyldiimidazole (0.72 g) in dry pyridine (8 ml) under nitrogen. The resulting solution was stirred under nitrogen for 3 hours at ambient temperature and then the volume of the solution was reduced by evaporation under reduced pressure. The residual syrup was diluted with aqueous acetone (50%, 20 ml) and the resultant solid

was collected, washed with water and acetone and dried to give a crude product (0.48 g). This material together with another crude sample (0.1 g, prepared in a similar manner as hereinbefore described) was recrystallised from acetic acid (ca 25 ml) by the addition of hot water (5 ml) to afford, after washing with acetic acid, water and ethanol and drying, the title compound, 0.4 g. m.p. 340-345°C dec., δ(DMSO-d<sub>6</sub>), 4.68 (m, 2H): 5.2-5.4 (m, 2H); 5.9-6.2 (m, 1H); 7.07-7.2, 7.4-7.55, 7.6-7.7 (m's, 4H); 10.9, 11.45 and 12.1 (broad singlets, 3H).

### Example 11

#### 2-(2-Propoxyphenyl)-6-purinone

A mixture of 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one (0.3 g), formamidine acetate (0.18 g) and anhydrous sodium acetate (0.1 g) was heated in an oil bath at 155°-165°C for 2½ hours. The mixture melted and then resolidified. Ethanol (1 ml) was added and the title compound was collected by filtration, 0.31 g, m.p. 256-258°C.

### Example 12

#### 2-(2-Propoxyphenyl)purine-6,8-dione

In a similar manner to Example 9 reaction of carbonyldiimidazole (4.98 g) with 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one (7.00 g) in toluene (350 ml) afforded the title compound, 3.76 g, m.p. >340°C (recrystallised from dimethylformamide).

### Example 13

Pharmaceutical compositions for oral administration are prepared by combining the following :

		%	w/w
30	2-(2-Propoxyphenyl)-6-purinone	0.5	3.0
35	2% w/w Soya lecithin in soya bean oil	90.45	88.2
40	Hydrogenated vegetable shortening and beeswax	9.05	8.8
			8.45

The formulations are then filled into individual soft gelatin capsules.

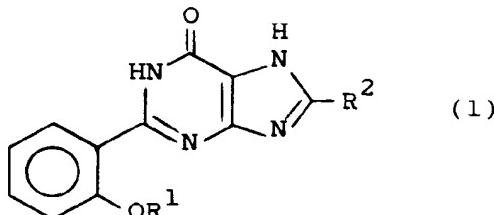
### Example 14

A pharmaceutical composition for parenteral administration is prepared by dissolving the title compound of Example 1 (0.02 g) in polyethylene glycol 300 (25 ml) with heating. This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

**Claims****Claims for the following Contracting State : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

5        1. A compound of the formula (1) :

10



15

or a pharmaceutically acceptable salt thereof, wherein

R¹ is C<sub>1-6</sub>alkyl or C<sub>2-6</sub>alkenyl, and

R² is hydrogen or hydroxy.

2. A compound according to claim 1 wherein R² is hydrogen.

20

3. A compound according to claim 1 wherein R² is hydroxy.

4. A compound according to any one of claims 1 to 3 wherein R¹ is C<sub>2-5</sub>alkyl.5. A compound according to any one of claims 1 to 3 wherein R¹ is C<sub>3-5</sub>alkenyl.

6. A compound according to claim 1 which is :

2-(2-propoxypyhenyl)-6-purinone,

25

2-(2-ethoxypyhenyl)-6-purinone,

2-(2-butoxypyhenyl)-6-purinone,

2-(2-isobutoxypyhenyl)-6-purinone,

2-(2-propoxypyhenyl)purine-6,8-dione,

2-(2-methoxypyhenyl)purine-6,8-dione,

30

2-(2-ethoxypyhenyl)purine-6,8-dione,

2-(2-butoxypyhenyl)purine-6,8-dione,

2-(2-isobutoxypyhenyl)purine-6,8-dione, or

2-(2-allyloxyphenyl)purine-6,8-dione

or a pharmaceutically acceptable salt thereof.

35

7. 2-(2-Propoxypyhenyl)-6-purinone or a pharmaceutically acceptable salt thereof.

8. 2-(2-Propoxypyhenyl)purine-6,8-dione or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8 for use as a medicament.

10. A compound according to any one of claims 1 to 8 for use as a bronchodilator.

11. A compound according to any one of claims 1 to 8 for use as a vasodilator.

40

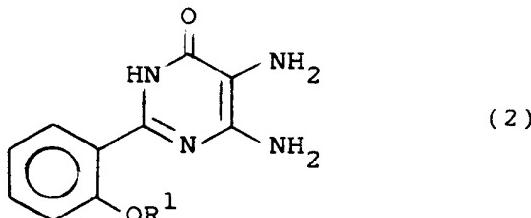
12. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

13. A process for preparing a compound of the formula (1) or a pharmaceutically acceptable salt thereof as defined in claim 1 which comprises :

a) for compounds wherein R² is hydrogen, reacting a compound of the formula (2) :

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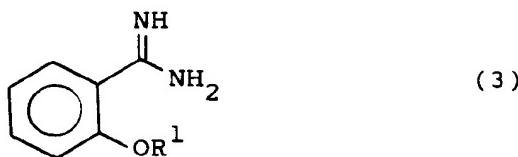
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wherein R¹ is as defined in claim 1, with a formylating agent;

b) for compounds wherein R² is hydroxy, reacting a compound of the formula (2) as hereinbefore defined with a carbonylating agent;

c) for compounds wherein R<sup>2</sup> is hydrogen, reacting a compound of the formula (3) :

5



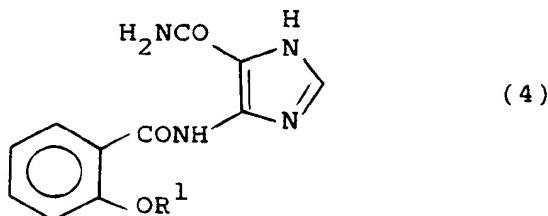
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wherein R<sup>1</sup> is as hereinbefore defined with 4-amino-5-imidazolecarboxamide,

d) for compounds wherein R<sup>2</sup> is hydrogen, cyclising a compound of the formula (4) :

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20

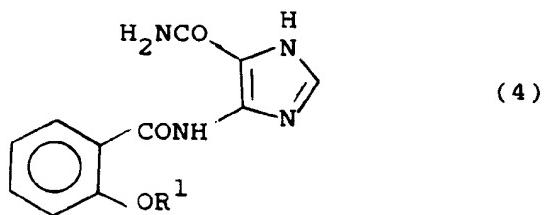


wherein R<sup>1</sup> is as hereinbefore defined; and thereafter optionally forming a pharmaceutically acceptable salt.

14. A compound of the formula (4) :

25

30



wherein R<sup>1</sup> is C<sub>1-6</sub>alkyl or C<sub>2-6</sub>alkenyl.

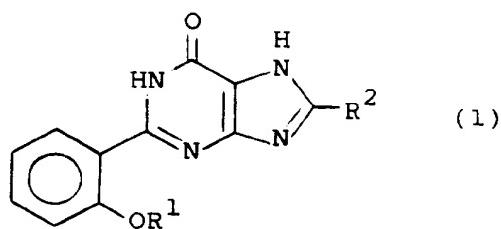
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**Claims for the following Contracting States : ES, GR**

1. A process for preparing a compound of the formula (1) :

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or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> is C<sub>1-6</sub>alkyl or C<sub>2-6</sub>alkenyl, and

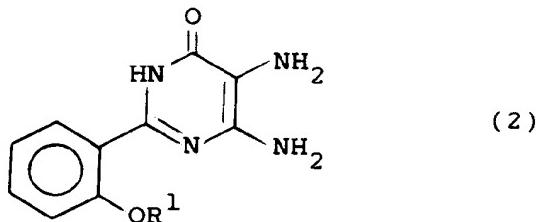
R<sup>2</sup> is hydrogen or hydroxy,

which process comprises :

a) for compounds wherein R<sup>2</sup> is hydrogen; reacting a compound of the formula (2) :

55

5

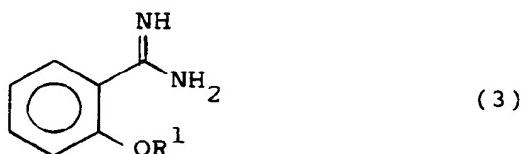


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- wherein R<sup>1</sup> is as hereinbefore defined, with a formylating agent;  
 b) for compounds wherein R<sup>2</sup> is hydroxy,  
 reacting a compound of the formula (2) as hereinbefore defined with a carbonylating agent;  
 c) for compounds wherein R<sup>2</sup> is hydrogen, reacting a compound of the formula (3) :

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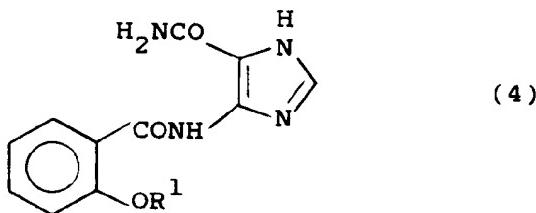
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- wherein R<sup>1</sup> is as hereinbefore defined with 4-amino-5-imidazolecarboxamide,  
 d) for compounds wherein R<sup>2</sup> is hydrogen, cyclising a compound of the formula (4) :

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wherein R<sup>1</sup> is as hereinbefore defined;

and thereafter optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 for preparing a compound wherein R<sup>2</sup> is hydrogen.
3. A process according to claim 1 for preparing a compound wherein R<sup>2</sup> is hydroxy.
4. A process according to any one of claims 1 to 3 for preparing a compound wherein R<sup>1</sup> is C<sub>2-5</sub>alkyl.
5. A process according to any one of claims 1 to 3 for preparing a compound wherein R<sup>1</sup> is C<sub>3-5</sub>alkenyl.

6. A process according to claim 1 for preparing a compound which is :

- 2-(2-propoxyphenyl)-6-purinone,
- 2-(2-ethoxyphenyl)-6-purinone,
- 2-(2-butoxyphenyl)-6-purinone,
- 2-(2-isobutoxyphenyl)-6-purinone,
- 2-(2-propoxyphenyl)purine-6,8-dione,
- 2-(2-methoxyphenyl)purine-6,8-dione,
- 2-(2-ethoxyphenyl)purine-6,8-dione,
- 2-(2-butoxyphenyl)purine-6,8-dione,
- 2-(2-isobutoxyphenyl)purine-6,8-dione, or

2-(2-allyloxyphenyl)purine-6,8-dione

or a pharmaceutically acceptable salt thereof.

7. A process according to claim 1 wherein a formylating agent is selected from formic acid, C<sub>1-4</sub>alkyl formate, formamide, C<sub>1-4</sub>alkyl formamide, formamidine, C<sub>1-4</sub>alkyl formamidine or tri(C<sub>1-4</sub>)alkyl orthoformate.

8. A process according to claim 1 wherein a carbonylating agent is selected from urea, di(C<sub>1-4</sub>)alkylcarbo-nate, C<sub>1-4</sub>alkyl chloroformate, phosgene, trichloromethyl chloroformate or carbonyldiimidazole.

9. A process for preparing 2-(2-propoxyphenyl)-6-purinone or a pharmaceutically acceptable salt thereof which comprises reacting 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one or an acid addition salt thereof with

formamide or formamidine acetate and optionally forming a pharmaceutically acceptable salt thereof.

10. A process for preparing 2-(2-propoxyphenyl)purine-6,8-dione or a pharmaceutically acceptable salt thereof which comprises reacting 4,5-diamino-2-(2-propoxyphenyl)pyrimidin-6-one with urea or carbonyldimidazole and optionally forming a pharmaceutically acceptable salt thereof.

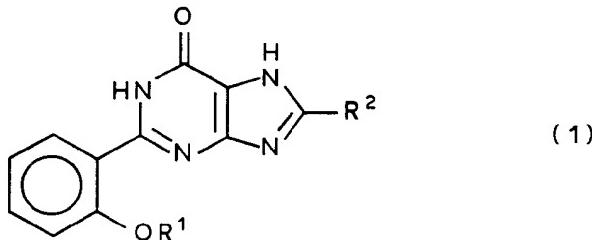
5 11. A process for preparing a pharmaceutical composition which comprises bringing into association a compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10 **Patentansprüche**

**Patentansprüche für folgende Vertragsstaaten :AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

15 1. Verbindung der Formel (1):

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oder ein pharmazeutisch verträgliches Salz davon, in der R¹ einen C<sub>1-6</sub>-Alkyl- oder einen C<sub>2-6</sub>-Alkenylrest bedeutet, und R² ein Wasserstoffatom oder eine Hydroxylgruppe ist.

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2. Verbindung gemäß Anspruch 1, wobei R² ein Wasserstoffatom bedeutet.

3. Verbindung gemäß Anspruch 1, wobei R² eine Hydroxylgruppe bedeutet.

4. Verbindung gemäß einem der Ansprüche 1 bis 3, wobei R¹ einen C<sub>2-5</sub>-Alkylrest bedeutet.

5. Verbindung gemäß einem der Ansprüche 1 bis 3, wobei R¹ einen C<sub>3-5</sub>-Alkenylrest bedeutet.

6. Verbindung gemäß Anspruch 1, die

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2-(2-Propoxyphenyl)-6-purinon

2-(2-Ethoxyphenyl)-6-purinon

2-(2-Butoxyphenyl)-6-purinon

2-(2-Isobutoxyphenyl)-6-purinon

2-(2-Propoxyphenyl)purin-6,8-dion

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2-(2-Methoxyphenyl)purin-6,8-dion

2-(2-Ethoxyphenyl)purin-6,8-dion

2-(2-Butoxyphenyl)purin-6,8-dion

2-(2-isobutoxyphenyl)purin-6,8-dion oder

2-(2-Allyloxyphenyl)purin-6,8-dion

oder ein pharmazeutisch verträgliches Salz davon bedeutet.

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7. 2-(2-Propoxyphenyl)-6-purinon oder ein pharmazeutisch verträgliches Salz davon.

8. 2-(2-Propoxyphenyl)purin-6,8-dion oder ein pharmazeutisch verträgliches Salz davon.

9. Verbindung gemäß einem der Ansprüche 1 bis 8 zur Verwendung als Arzneimittel.

10. Verbindung gemäß einem der Ansprüche 1 bis 8 zur Verwendung als Bronchodilatator.

11. Verbindung gemäß einem der Ansprüche 1 bis 8 zur Verwendung als Vasodilatator.

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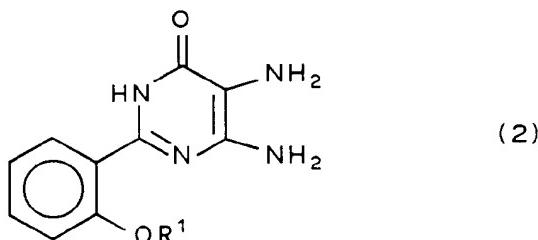
12. Arzneimittel, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 8 und einen pharmazeutisch verträglichen Träger.

13. Verfahren zur Herstellung einer Verbindung der Formel (1) oder eines pharmazeutisch verträglichen Salzes davon, wie in Anspruch 1 definiert, umfassend:

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a) für Verbindungen, in denen R² ein Wasserstoffatom bedeutet, die Umsetzung einer Verbindung der Formel (2):

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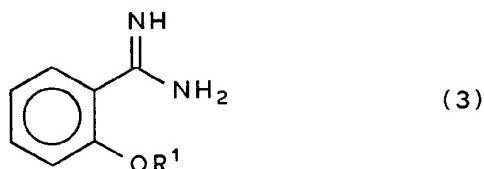


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- a) in der R<sup>1</sup> wie in Anspruch 1 definiert ist, mit einem Formylierungsmittel,
- b) für Verbindungen, in denen R<sup>2</sup> eine Hydroxylgruppe bedeutet, die Umsetzung einer Verbindung der Formel (2), wie vorstehend definiert, mit einem Carbonylierungsmittel,
- c) für Verbindungen, in denen R<sup>2</sup> ein Wasserstoffatom bedeutet, die Umsetzung einer Verbindung der Formel (3):

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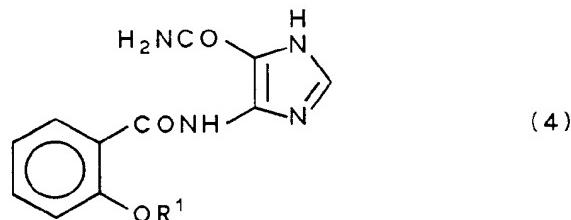


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- d) in der R<sup>1</sup> wie vorstehend definiert ist, mit 4-Amino-5-imidazolcarboxamid,
- e) für Verbindungen, in denen R<sup>2</sup> ein Wasserstoffatom bedeutet, die Cyclisierung einer Verbindung der Formel (4):

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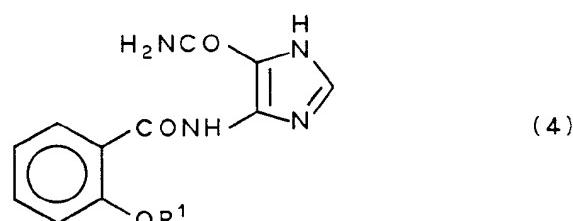


in der R<sup>1</sup> wie vorstehend definiert ist, und danach gegebenenfalls die Bildung eines pharmazeutisch verträglichen Salzes.

14. Verbindung der Formel (4):

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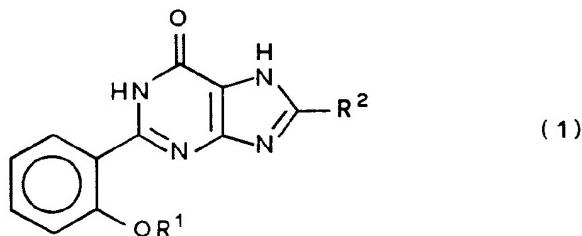
in der R<sup>1</sup> einen C<sub>1-6</sub>-Alkyl- oder einen C<sub>2-6</sub>-Alkenylrest bedeutet.

**Patentansprüche für folgenden Vertragsstaaten : ES, GR**

1. Verfahren zur Herstellung einer Verbindung der Formel (1):

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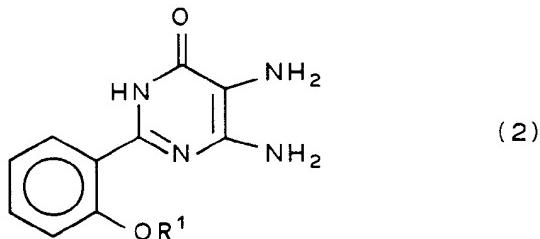
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oder eines pharmazeutisch verträglichen Salzes davon, in der R<sup>1</sup> einen C<sub>1-6</sub>-Alkyl- oder einen C<sub>2-6</sub>-Alkenylrest bedeutet, und R<sup>2</sup> ein Wasserstoffatom oder eine Hydroxylgruppe ist, welches Verfahren

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a) für Verbindungen, in denen R<sup>2</sup> ein Wasserstoffatom bedeutet, die Umsetzung einer Verbindung der Formel (2):

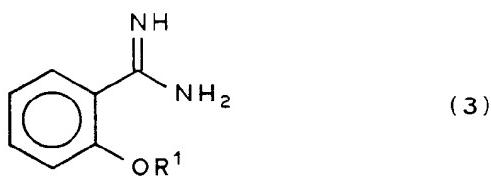
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in der R<sup>1</sup> wie vorstehend definiert ist, mit einem Formylierungsmittel,  
b) für Verbindungen, in denen R<sup>2</sup> eine Hydroxylgruppe bedeutet, die Umsetzung einer Verbindung der Formel (2), wie vorstehend definiert, mit einem Carbonylierungsmittel,  
c) für Verbindungen, in denen R<sup>2</sup> ein Wasserstoffatom bedeutet, die Umsetzung einer Verbindung der Formel (3):

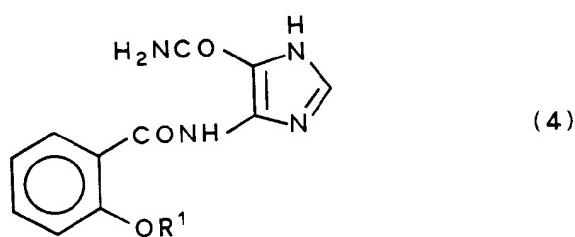
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in der R<sup>1</sup> wie vorstehend definiert ist, mit 4-Amino-5-imidazolcarboxamid,  
d) für Verbindungen, in denen R<sup>2</sup> ein Wasserstoffatom bedeutet, die Cyclisierung einer Verbindung der Formel (4):

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in der R<sup>1</sup> wie vorstehend definiert ist, und danach gegebenenfalls die Bildung eines pharmazeutisch verträglichen Salzes umfaßt.  
2. Verfahren gemäß Anspruch 1 zur Herstellung einer Verbindung, in der R<sup>2</sup> ein Wasserstoffatom bedeutet.  
3. Verfahren gemäß Anspruch 1 zur Herstellung einer Verbindung, in der R<sup>2</sup> eine Hydroxylgruppe bedeutet.

4. Verfahren gemäß einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, in der R<sup>1</sup> einen C<sub>2-5</sub>-Alkylrest bedeutet.

5. Verfahren gemäß einem der Ansprüche 1 bis 3 zur Herstellung einer Verbindung, in der R<sup>1</sup> einen C<sub>3-5</sub>-Alkenylrest bedeutet.

6. Verfahren gemäß Anspruch 1, zur Herstellung einer Verbindung, die:

2-(2-Propoxyphenyl)-6-purinon

2-(2-Ethoxyphenyl)-6-purinon

2-(2-Butoxyphenyl)-6-purinon

2-(2-Isobutoxyphenyl)-6-purinon

10 2-(2-Propoxyphenyl)purin-6,8-dion

2-(2-Methoxyphenyl)purin-6,8-dion

2-(2-Ethoxyphenyl)purin-6,8-dion

2-(2-Butoxyphenyl)purin-6,8-dion

15 2-(2-Isobutoxyphenyl)purin-6,8-dion oder

2-(2-Allyloxyphenyl)purin-6,8-dion

oder ein pharmazeutisch verträgliches Salz davon bedeutet.

7. Verfahren gemäß Anspruch 1, wobei ein Formylierungsmittel aus Ameisensäure, C<sub>1-4</sub>-Alkylformiat, Formamid, C<sub>1-4</sub>-Alkylformamid, Formamidin, C<sub>1-4</sub>-Alkylformamidin oder Tri(C<sub>1-4</sub>)alkylorthoformiat ausgewählt wird.

20 8. Verfahren gemäß Anspruch 1, wobei ein Carbonylierungsmittel aus Harnstoff, Di(C<sub>1-4</sub>)alkylcarbonat, C<sub>1-4</sub>-Alkylchlorformiat, Phosgen, Trichlormethylchlorformiat oder Carbonyldiimidazol ausgewählt wird.

9. Verfahren zur Herstellung von 2-(2-Propoxyphenyl)-6-purinon oder eines pharmazeutisch verträglichen Salzes davon, umfassend die Umsetzung von 4,5-Diamino-2-(2-propoxyphenyl)pyrimidin-6-on oder einem Säureadditionssalz davon mit Formamid oder Formamidinacetat und gegebenenfalls die Bildung eines pharmazeutisch verträglichen Salzes davon.

25 10. Verfahren zur Herstellung von 2-(2-Propoxyphenyl)purin-6,8-dion oder eines pharmazeutisch verträglichen Salzes davon, umfassend die Umsetzung von 4,5-Diamino-2-(2-propoxyphenyl)pyrimidin-6-on mit Harnstoff oder Carbonyldiimidazol und gegebenenfalls die Bildung eines pharmazeutisch verträglichen Salzes davon.

30 11. Verfahren zur Herstellung eines Arzneimittels, umfassend die Vereinigung einer Verbindung der Formel (1), wie in Anspruch 1 definiert, oder eines pharmazeutisch verträglichen Salzes davon und eines pharmazeutisch verträglichen Trägers.

### Revendications

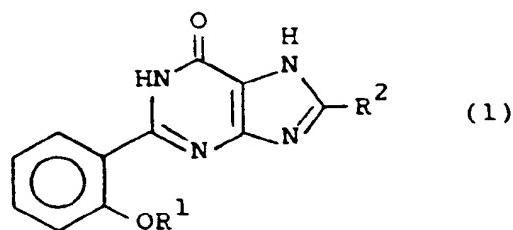
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**Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE**

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1. composé de formule (1):

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ou un de ses sels pharmaceutiquement acceptables, dans laquelle

R<sup>1</sup> est un groupe alkyle en C<sub>1-6</sub> ou alcényle en C<sub>2-6</sub>, et

R<sup>2</sup> est un atome d'hydrogène ou un groupe hydroxy.

2. Composé selon la revendication 1, dans lequel R<sup>2</sup> est un atome d'hydrogène.

3. Composé selon la revendication 1, dans lequel R<sup>2</sup> est un groupe hydroxy.

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4. composé selon l'une quelconque des revendications 1 à 3, dans lequel R<sup>1</sup> est un groupe alkyle en C<sub>2-5</sub>.

5. Composé selon l'une quelconque des revendications 1 à 3, dans lequel R<sup>1</sup> est un groupe alcényle en

C<sub>3-5</sub>.

6. Composé selon la revendication 1 qui est :

la 2-(2-propoxyphényl)-6-purinone,

la 2-(2-éthoxyphényl)-6-purinone,

5 la 2-(2-butoxyphényl)-6-purinone,

la 2-(2-isobutoxyphényl)-6-purinone,

la 2-(2-propoxyphényl)purine-6,8-dione,

la 2-(2-méthoxyphényl)purine-6,8-dione,

la 2-(2-éthoxyphényl)purine-6,8-dione,

10 la 2-(2-butoxyphényl)purine-6,8-dione,

la 2-(2-isobutoxyphényl)purine-6,8-dione ou

la 2-(2-allyloxyphényl)purine-6,8-dione

ou un de ses sels pharmaceutiquement acceptables.

7. 2-(2-propoxyphényl)-6-purinone ou un de ses sels pharmaceutiquement acceptables.

15 8. 2-(2-propoxyphényl)purine-6,8-dione ou un de ses sels pharmaceutiquement acceptables.

9. Composé selon l'une quelconque des revendications 1 à 8 pour l'utilisation comme médicament.

10. Composé selon l'une quelconque des revendications 1 à 8 pour l'utilisation comme bronchodilatateur.

11. Composé selon l'une quelconque des revendications 1 à 8 pour l'utilisation comme vasodilatateur.

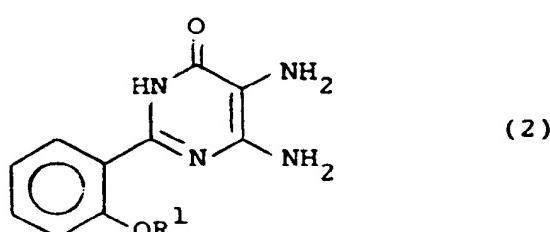
12. Composition pharmaceutique qui comprend un composé selon l'une quelconque des revendications

20 1 à 8 et un véhicule pharmaceutiquement acceptable.

13. Procédé pour préparer un composé de formule (1) ou un de ses sels pharmaceutiquement acceptables comme définis dans la revendication 1, qui comprend :

a) pour les composés dans lesquels R<sup>2</sup> est un atome d'hydrogène, la réaction d'un composé de formule (2) :

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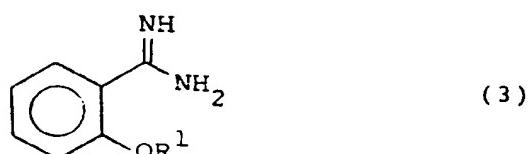
dans laquelle R<sup>1</sup> est comme défini dans la revendication 1, avec un agent de formylation ;

b) pour les composés dans lesquels R<sup>2</sup> est un groupe hydroxy, la réaction d'un composé de formule (2) comme précédemment défini avec un agent de carbonylation ;

c) pour les composés dans lesquels R<sup>2</sup> est un atome d'hydrogène, la réaction d'un composé de formule

40 (3) :

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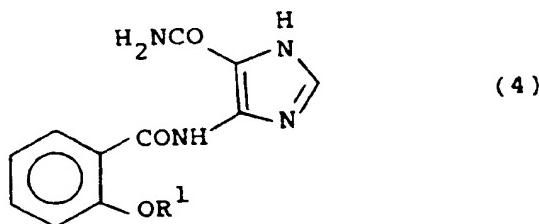
dans laquelle R<sup>1</sup> est comme précédemment défini avec le 4-amino-5-imidazolecarboxamide,

d) pour les composés dans lesquels R<sup>2</sup> est un atome d'hydrogène,

la cyclisation d'un composé de formule (4) :

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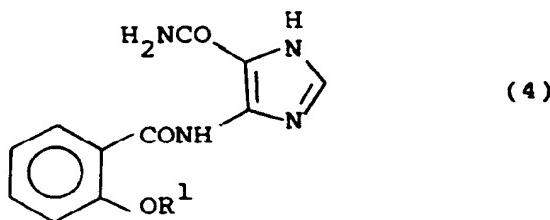


10 dans laquelle R<sup>1</sup> est comme précédemment défini ; puis, facultativement, la formation d'un sel pharmaceutiquement acceptable.

14. Composé de formule (4) :

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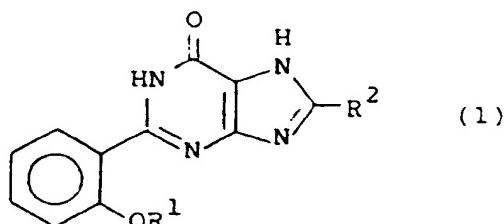
dans laquelle R<sup>1</sup> est un groupe alkyle en C<sub>1-6</sub> ou alcényle en C<sub>2-6</sub>.

25 **Revendications pour les Etats contractants suivants : ES, GR**

1. Procédé pour la préparation d'un composé de formule (1) :

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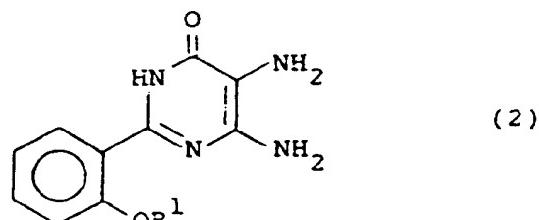
ou un de ses sels pharmaceutiquement acceptables, dans laquelle R<sup>1</sup> est un groupe alkyle en C<sub>1-6</sub> ou alcényle en C<sub>2-6</sub>, et

40 R<sup>2</sup> est un atome d'hydrogène ou un groupe hydroxy, lequel procédé comprend :

a) pour les composés dans lesquels R<sup>2</sup> est un atome d'hydrogène, la réaction d'un composé de formule (2) :

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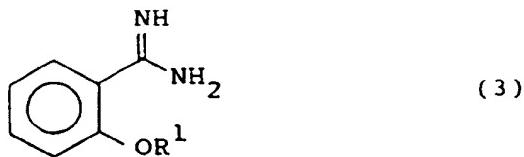


dans laquelle R<sup>1</sup> est comme précédemment défini, avec un agent de formylation ;

b) pour les composés dans lesquels R<sup>2</sup> est un groupe hydroxy, la réaction d'un composé de formule (2) comme précédemment défini avec un agent de carbonylation ;

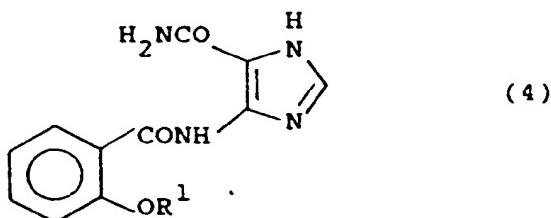
c) pour les composés dans lesquels R<sup>2</sup> est un atome d'hydrogène, la réaction d'un composé de formule (3) :

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20 dans laquelle R<sup>1</sup> est comme précédemment défini ; puis, facultativement, la formation d'un sel pharmaceutiquement acceptable.

2. Procédé selon la revendication 1 pour préparer un composé dans lequel R<sup>2</sup> est un atome d'hydrogène.
3. Procédé selon la revendication 1 pour préparer un composé dans lequel R<sup>2</sup> est un groupe hydroxy.
4. Procédé selon l'une quelconque des revendications 1 à 3 pour préparer un composé dans lequel R<sup>1</sup> est

25 un groupe alkyle en C<sub>2-5</sub>.

5. Procédé selon l'une quelconque des revendications 1 à 3 pour préparer un composé dans lequel R<sup>1</sup> est un groupe alcényle en C<sub>3-5</sub>.

6. Procédé selon la revendication 1 pour préparer un composé qui est :

la 2-(2-propoxyphényl)-6-purinone,  
 30 la 2-(2-éthoxyphényl)-6-purinone,  
 la 2-(2-butoxyphényl)-6-purinone,  
 la 2-(2-isobutoxyphényl)-6-purinone,  
 la 2-(2-propoxyphényl)purine-6,8-dione,  
 la 2-(2-méthoxyphényl)purine-6,8-dione,  
 35 la 2-(2-éthoxyphényl)purine-6,8-dione,  
 la 2-(2-butoxyphényl)purine-6,8-dione,  
 la 2-(2-isobutoxyphényl)purine-6,8-dione ou  
 la 2-(2-allyloxyphényl)purine-6,8-dione  
 ou un de ses sels pharmaceutiquement acceptables.

40 7. Procédé selon la revendication 1, dans lequel l'agent de formylation est choisi parmi l'acide formique, un formiate d'alkyle en C<sub>1-4</sub>, le formamide, un (alkyl en C<sub>1-4</sub>) formamide, la formamidine, une (alkyl en C<sub>1-4</sub>) formamidine ou un orthoformiate de tri(alkyle en C<sub>1-4</sub>).

45 8. Procédé selon la revendication 1, dans lequel l'agent de carbonylation est choisi parmi l'urée, un carbonate de di(alkyle en C<sub>1-4</sub>), un chloroformiate d'alkyle en C<sub>1-4</sub>, le phosgène, le chloroformiate de trichlorométhyle ou le carbonyldiimidazole.

9. Procédé pour préparer la 2-(2-propoxyphényl)-6-purinone ou un de ses sels pharmaceutiquement acceptables, qui comprend la réaction de la 4,5-diamino-2-(2-propoxyphényl)pyrimidine-6-one ou d'un de ses sels d'addition d'acides avec le formamide ou l'acétate de formamidine et facultativement la formation d'un sel pharmaceutiquement acceptable correspondant.

50 10. Procédé pour préparer la 2-(2-propoxyphényl)purine-6,8-dione ou un de ses sels pharmaceutiquement acceptables, qui comprend la réaction de la 4,5-diamino-2-(2-propoxyphényl)pyrimidine-6-one avec l'urée ou le carbonyldiimidazole et facultativement la formation d'un sel pharmaceutiquement acceptable correspondant.

11. Procédé pour préparer une composition pharmaceutique, qui comprend l'association d'un composé de formule (1) comme défini dans la revendication 1 ou d'un de ses sels pharmaceutiquement acceptables et d'un véhicule pharmaceutiquement acceptable.